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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants :	Pickar *et al.*	Confirmation No:	5912
Serial Number:	10/629,123	Examiner:	Layla Soroush
Filing Date :	July 28, 2003	Art Unit:	1617

For : NOVEL ANTIPSYCHOTIC COMBINATION THERAPIES AND COMPOSITIONS USEFUL THEREIN

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. DAVID PICKAR UNDER 37 CFR 1.132

I, David Pickar do hereby declare that:

1. I graduated from Yale University School of Medicine in 1973 with a degree in Medicine (MD).

2. I am a co-inventor of the claimed invention in the above-referenced application.

3. I have reviewed the Final Office Action mailed on December 28, 2007 and the obviousness rejection made of claims 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67, therein. I have also reviewed Pickar *et al.* U.S. Patent No. 5,492,907 ("Pickar") and Beasley, Jr. *et al.* U.S. Patent No. 5,605,897 ("Beasley"). After reviewing these references, I believe that one of ordinary skill in the art would not have a reasonable expectation of success for the invention of a method of treating a serious psychotic mental illness by administering a combination of an α_2-adrenergic receptor antagonist and an atypical antipsychotic neuroleptic to a patient in need of such treatment in light of the teachings of Pickar and Beasley.

4. Pickar does not teach the treatment of a serious psychotic mental illness with a combination of an α_2- adrenergic receptor antagonist with an atypical antipsychotic. Pickar teaches the combination of an α_2-adrenergic receptor antagonist and a D_2 receptor antagonist for the treatment of a serious psychotic mental illness.[1] Pickar explains that drugs with a mechanism of action of D_2 antagonism (D_2 antagonists or D_2 blockers) are known as conventional or "typical antipsychotics"[2] and that a "significant" number of patients have proven resistant to treatment with such "typical antipsychotic" drugs.[3] The unexpected finding described in Pickar is that the addition of an α_2- adrenergic receptor antagonist to a "typical antipsychotic" (*i.e.*, the D_2 blocker, fluphenazine)[4] resulted in improvement beyond the response

[1] *See* Pickar at the Abstract.
[2] *Id.* at column 1; lines 10-14.
[3] *Id.* at column 1; lines 18-35.
[4] *Id.* at column 4; lines 20-30.

to the "typical antipsychotic" (D_2 blocker) alone.[5] Pickar does not teach the combination of an α_2-adrenergic receptor antagonist added to "atypical antipsychotic" drugs such as olanzapine with mechanisms of action including both D_2 blocking effects and antagonism of the 5-HT-2 receptor. One of ordinary skill in the art would not equate D_2 blockers with D_2/5HT-2 blockers (serotonin – dopamine antagonists)[6] as the Examiner reasons.

5. Beasley does not suggest the replacement of the typical antipsychotic of Pickar with an atypical antipsychotic. Beasley teaches, as is well known in the art, that olanzapine "shows its greatest activity at the 5-HT-2 receptor."[7] It is widely known that the mechanism of action of olanzapine and other "atypical antipsychotics" with disorders of the central nervous system is through antagonism of the 5-HT-2 receptor in conjunction with antagonism of the D_2 receptor.[8]

6. One of ordinary skill in the art would not have expected atypical antipsychotics, like olanzapine to be effective in combination with an α_2-adrenergic receptor antagonist, let alone have improved function as is demonstrated in the above-referenced patent application based on the teachings of Pickar and Beasley and the knowledge of one of ordinary skill in the art. It is well known in the art that atypical psychotics have their greatest activity at the 5-HT-2 receptor and not at the D_2 receptor.[9] This difference in D_2 receptor occupancy between typical and atypical antipsychotics has clinical relevance. For example, when D_2 occupancy exceeds a threshold in the range of 75%-80% of D_2 receptor occupancy, extrapyramidal symptoms can result.[10] Atypical antipsychotics have lower D_2 occupancy than this threshold.[11] For example, clozapine has 20%-67%.[12] Moreover, atypical antipsychotics (or second generation antipsychotics) have different clinical effects from typical antipsychotics (or first generation antipsychotics) in patients with schizophrenia.[13] Thus, one of ordinary skill in the art would know that there are significant differences in the mechanism of typical and atypical antipsychotics and that these differences has clinical relevance.

7. The results shown in the present application are unexpected in light of the teachings of Pickar and Beasley. Beasley teaches that olanzapine inhibited conditioned

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[5] *Id.* at Figure 1.
[6] *See* Kapur S, Remington G. Serotonin –dopamine interaction and its relevance to schizophrenia. American Journal of Psychiatry 1996; 153:466-476; Meltzer HY, *et al.* Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2, and serotonin-2 PK values. J Pharmacol Exp Therapeutics (1989) 251:238-246; Physician Desk Reference. 2007 – label for Zyprexa, p 1830 Under the heading for clinical pharmacology; Stockmeier CA *et al.* Characterization of typical and atypical antipsychotic drugs based on in vivo occupancy of serotonin and dopamine receptors. J Pharmacol Exp Therapeutics 1993;266:1374-1384; and Davis *et al.* A meta-analysis of the efficacy of second-generation antipsychotics. Arch. Gen. Psychiatry 60:553-564 (June 2003), attached as Exhibits 1-5, herewith.
[7] *See* Beasley at column 12, lines 37-42.
[8] *See* Exhibits 1-4, filed herewith and and Beasley at column 12, lines 33-42.
[9] *See* Exhibit 2 at the Abstract, page 242, first four lines of paragraph bridging columns 1 and 2, and Exhibit 3 at the Abstract, page 1374, first 3 lines of column 2, page 1377 Table 1, page 1378, first 6 lines of the Discussion, page 1380, first four lines of paragraph bridging columns 1 and 2, and page 1382, column 2, lines 9-13.
[10] *See* Exhibit 1 at page 470, first paragraph in "Extrapyramidal Symptoms" section.
[11] *Id.*
[12] *Id.*
[13] *See* Exhibit 5 at the Background and page 553 column 1.

avoidance response in rats in the dose range of 4-7 mg/kg.[14] Conditioned avoidance response is a standard behavioral test predictive of antipsychotic activity. One of ordinary skill in the art would not have expected that the addition of the α_2-adrenergic receptor antagonist idazoxan to olanzapine would reduce the dose required for inhibition of conditioned avoidance response to 2.5 mg/kg as shown in the above-referenced patent application. This is because of the mechanical and clinical differences between typical and atypical antipsychotics described above. This unexpected finding, neither predicted nor contemplated by Beasley or Pickar, has direct implications for antipsychotic therapeutics, including enhanced efficacy and dosage reduction, as shown in the present application.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

David Pickar

Dated: 5/27/08

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[14] *See* Beasley at column 11, lines 11-27.